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Vitamin D in youth with Type 1 diabetes: prevalence of insufficiency and association with insulin resistance in the SEARCH Nutrition Ancillary Study

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Abstract

Aims—To determine the prevalence of plasma vitamin D insufficiency in individuals with Type 1 diabetes and to determine the cross-sectional and longitudinal associations of plasma vitamin D with insulin resistance.

Methods—Participants from the SEARCH for Diabetes in Youth Study [n = 1426; mean age 11.2 years (SD 3.9)] had physician-diagnosed Type 1 diabetes [diabetes duration mean 10.2 months (SD 6.5)] with data available at baseline and follow-up (approximately 12 and 24 months after baseline). Insulin resistance was estimated using a validated equation. Cross-sectional and longitudinal multivariate logistic regression models were used to determine the association of plasma vitamin D with insulin resistance, adjusting for potential confounders.

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Competing interests

None declared.

Results—Forty-nine per cent of individuals had plasma vitamin D < 50 nmol/l and 26% were insulin resistant. In cross-sectional multivariate analyses, participants who had higher plasma vitamin D (65 nmol/l) had lower odds of prevalent insulin resistance than participants with lower plasma vitamin D (25 nmol/l) (odds ratio 0.70, 95% CI 0.57–0.85). This association was attenuated after additional adjustment for BMI z-score, which could be a confounder or a mediator (odds ratio 0.81, 95% CI 0.64–1.03). In longitudinal multivariate analyses, individuals with higher plasma vitamin D at baseline had lower odds of incident insulin resistance, but this was not significant (odds ratio 0.85, 95% CI 0.63–1.14).

Conclusions—Vitamin D insufficiency is common in individuals with Type 1 diabetes and may increase risk for insulin resistance. Additional prospective studies are needed to determine the association between plasma vitamin D and insulin resistance, and to further examine the role of adiposity on this association.

Introduction

Beta-cell loss and absolute insulin deficiency are the primary issues facing individuals with Type 1 diabetes. However, a growing percentage of these youth are overweight and obese [1], which is concerning given the relationship between obesity and insulin resistance [2]. Moreover, approximately 20% of individuals with Type 1 diabetes are insulin resistant [3]. Given that insulin resistance increases cardiovascular risk [4], the identification of modifiable factors that improve insulin resistance may be critical for maintaining glycaemic control and improving long-term health outcomes in individuals with Type 1 diabetes.

The mechanisms underlying the relationship between vitamin D and insulin resistance are not completely understood. 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], the biologically active form of vitamin D, has been shown to enhance insulin-mediated glucose transport [5] and activate the transcription of the insulin receptor gene [6]. Further, vitamin D receptors are expressed in skeletal and adipose tissues [7], main sites of peripheral glucose uptake. Findings from epidemiological studies have been mixed with inverse [8–13] and null [11,14,15] associations reported. Given discrepant findings, the prevalence of obesity and insulin resistance among youth with Type 1 diabetes and the potential contribution of insulin resistance to cardiovascular risk in this vulnerable population, additional studies are needed.

The SEARCH for Diabetes in Youth (SEARCH) study provides a unique opportunity to explore the potential role of vitamin D in a large ethnically and regionally diverse cohort of youth with clinically diagnosed Type 1 diabetes. US data suggest a high prevalence of inadequate vitamin D levels in children [16], thus our aims were to determine the prevalence of low concentrations of 25-dihydroxyvitamin D [25(OH)D, the indicator of vitamin D status] in individuals with Type 1 diabetes and to determine the cross-sectional association of 25(OH)D with insulin resistance. We hypothesized that higher levels of 25(OH)D levels would be inversely associated with insulin resistance. Further we aimed to investigate the association of 25(OH)D with incident insulin resistance, hypothesizing that individuals with higher levels of 25(OH)D would be less likely to become insulin resistance than individuals with lower levels of 25(OH)D.

Subjects and methods

Overview

Data for this study derive from the SEARCH Study and the SEARCH Nutrition Ancillary Study. The parent SEARCH study [17,18] ascertained cases of diabetes diagnosed when subjects were < 20 years of age, starting in 2002 and continuing through to the present. Participants with newly diagnosed diabetes in 2002–2005 were invited to participate in a baseline research visit (mean diabetes duration at visit 10.5 months) and two follow-up visits approximately 12 and 24 months after their baseline visit. At each research visit, fasting blood samples were obtained from metabolically stable participants (defined as no episode of diabetic ketoacidosis during the previous month), physical measurements were conducted and questionnaires were administered. For SEARCH participants with Type 1 diabetes diagnosed in 2002–2005, SEARCH Nutrition Ancillary Study collected additional nutritional data, including plasma measures of 25(OH)D (nmol/l) obtained from frozen samples (stored at −80 °C) collected at the baseline and first follow-up SEARCH visits. Both studies were reviewed and approved annually by the local Institutional Review Board(s) that had jurisdiction over the local study population and complied with the Health Insurance Portability and Accountability Act. All participants provided informed consent and/or assent.

SEARCH data

Fasting blood samples were analysed to measure diabetes autoantibodies, HbA_{1c} and lipids. Glutamic acid decarboxylase 65 (GAD65) and insulinoma-associated 2 (IA-2) diabetes autoantibodies were analysed using a standardized protocol and a common serum calibrator developed by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)-sponsored standardization group [19]. Cut-off values for positivity were GAD65 ≥ 33 NIDDKU/ml and IA-2 5 ≥ NIDDKU/ml for IA-2 [19]. HbA_{1c} was measured in whole blood with an automated non-porous ion-exchange high-performance liquid chromatography system (model G-7; Tosoh Bioscience Inc., San Francisco, CA, USA). Lipid measurements, including triglycerides, were performed using Roche reagent on a Roche Modular-P Autoanalyzer (Roche Diagnostics, Indianapolis, IN, USA). Human leucocyte antigen class II genotyping (HLA DR/DQ) was performed with a PCR-based sequence-specific oligonucleotide probe system in the laboratories of the University of Washington (Seattle, WA, USA) and Roche Molecular Systems Pleasanton, CA, USA).

BMI (kg/m^2) z-scores from measured height and weight were derived for age and gender using the US Centers for Disease Control and Prevention (CDC) National Center for Health Statistics growth charts [20]. Waist circumference was measured using the National Health and Nutrition Examination Survey (NHANES) III protocol [21].

A surrogate measure of insulin resistance, appropriate for youth with Type 1 diabetes, was derived from the following equation: Insulin sensitivity score = exp[4.64725 − 0.02032*(waist circumference, cm) − 0.09779 × (HbA_{1c}, − 0.00235 × (triglyceride, mg/dl)]. A detailed description of the development and validation of this equation has been published elsewhere [22]. Briefly, a subset of participants from SEARCH(n = 85; ages 12–19 years)

underwent a 3-h euglycaemic–hyperinsulinaemic clamp to measure glucose disposal rate. Multivariate linear regression was used to estimate a surrogate measure insulin sensitivity score, with waist circumference explaining 60% of the variance in measured glucose disposal rate. The formula was reproduced and validated in youth with diabetes (Type 1 and Type 2) and healthy control subjects. Consistent with previous SEARCH analysis [3], the insulin sensitivity score was dichotomized to define insulin resistance (< 8.15) and insulin sensitivity (≥ 8.15).

Self-reported race and ethnicity were collected using 2000 US Census questions and, for this analysis, categorized as non-Hispanic white, African-American and 'other' [23]. Information about treatment regimen, including type(s) of insulin, total daily insulin dose, frequency of insulin injections or use of continuous subcutaneous insulin infusion (insulin pump) were also collected.

For participants ages ≥ 10 years, SEARCH ascertained physical activity status and pubertal development via questionnaire [24]. Moderate to vigorous physical activity was defined as ≥ 3 days/week of any activity that either tones or makes one sweat. Pubertal development was self-reported using the standard technique described by Marshall and Tanner [25,26]. For a sensitivity analysis, participants who were aged < 10 years were assumed to be prepubertal.

SEARCH Nutrition Ancillary Study data

25(OH)D was measured using the direct, competitive chemiluminescence immunoassay developed by Dia Sorin (Stillwater, MN, USA) [universal naming convention (UNC) detectable range, 5–320 nmol/l; intra-assay coefficient of variation, 11.0%], based on a linkage between specific vitamin D antibody coated magnetic particles and an isoluminol derivative. This method uses an antibody as a primary binding agent and measures $25(OH)D_2$ and $25(OH)D_3$ [27]. There were $n = 12$ at baseline and $n = 3$ at follow-up, with 25(OH)D values below the detectable limit and set to 4.9 nmol/l for this analysis. For descriptive analysis, 25(OH)D was categorized as: (1) risk of deficiency (< 30.0); (2) risk of inadequacy (30.0–49.9); (3) sufficient (50.0–125.0); and (4) possibly harmful (> 125.0) [28]. For multivariate analysis, 25(OH)D was utilized as a continuous variable.

Participant inclusion

'Type 1 diabetes' was defined by physicians' report of 'Type 1', 'Type 1a' or 'Type 1b' diabetes. Cross-sectional analysis included data from individuals with Type 1 diabetes who had measurements of 25(OH)D and an insulin sensitivity score at baseline, resulting in an analytic sample of 1426 individuals. For longitudinal analyses, participants from the cross-sectional analytic sample who had insulin resistance data at the 12- and/or 24-month follow-up visits were selected for inclusion. Given our interest in determining the association between 25(OH)D and incident insulin resistance, participants who were insulin resistant at baseline were excluded, resulting in a longitudinal sample of 735 participants. For participants who had measures of insulin resistance from two follow-up visits, data from their 24-month follow-up visit was used.

Statistical analyses

Analyses were performed using SAS (version 9.2; SAS Institute, Cary, NC, USA), with $P < 0.05$ indicating significance, except where otherwise stated. Comparisons of baseline percentages and mean values by participant characteristics were examined using χ^2-tests and analysis of variance (ANOVA). Trends in exposure and outcomes were examined using paired *t*-tests and multiple linear regression in the sub-population of individuals who had measurements at both baseline and follow-up and were not insulin resistance at baseline.

To determine the association of 25(OH)D with insulin resistance at baseline, a series of multivariate logistic regression models were fitted, first adjusted for diabetes duration only, then for covariates shown to be associated with 25(OH)D and/or insulin resistance (age, gender, race/ethnicity, HLA genotype, insulin regimen, clinical site and season of visit). Although pubertal status and physical activity may also be confounders, these data were collected in participants aged ≥ 10 years only and we wanted to retain the full, larger sample for primary analyses. Thus, pubertal status and physical activity were included in subsequent separate models for the subset of individuals with these measures. Further, previous research suggests that adiposity may be a mediator and/or confounder of the association between 25(OH)D and insulin resistance; consequently, additional analyses were conducted including BMI z-score in the full, larger sample. Finally, we had an a priori interest in determining whether the association between 25(OH)D and insulin resistance varied by disease duration, age, HLA genotype, race/ethnicity and BMI z-score; thus, we examined effect modification using separate interaction terms and likelihood ratio tests ($P < 0.1$). To facilitate clinical interpretation, odds ratios and 95% confidence intervals were obtained by comparing a difference of 40 nmol/l in 25(OH)D, which reflects a comparison between being at risk for 25(OH)D deficiency (25 nmol/l) and being sufficient for 25(OH)D (65 nmol/l).

Using the longitudinal sample to determine if baseline 25(OH)D is associated with incident insulin resistance, we used a similar series of multivariate logistic regression models to that of the cross-sectional models, but also included the change in time-varying covariates. As with the cross-sectional models, the estimated odds ratio and 95% confidence intervals reflect the odds of incident insulin resistance, given a 40 nmol/l change in 25(OH)D.

As the use of a dichotomous cut point to define insulin resistance would reduce our power to identify a small association, we repeated all multivariate analysis using linear regression to determine the relation between 25(OH)D and the continuous insulin sensitivity score. Finally, for a sensitivity analysis, all multivariate analyses were repeated in the subsample of participants who had physician-diagnosed Type 1 diabetes and had at least one instance of positive diabetes autoantibodies (GAD65 or IA-2: $n = 1211$).

Results

Cross-sectional sample

Forty-nine per cent of individuals were at risk of deficiency or at risk of insufficiency for vitamin D [25(OH)D < 50.0 nmol/l]. Compared with those who were vitamin D sufficient, these participants were more likely to be non-white, older at baseline and to have had their

research visit during the winter months (Table 1; all $P < 0.05$). They also tended to have lower insulin sensitivity scores, and higher BMI z-scores, triglycerides and waist circumference (all $P < 0.05$). Individuals with insulin resistance were older, had lower 25(OH)D, longer diabetes duration and higher BMI z-score, HbA_{1c}, triglycerides and waist circumference (Table 2; all $P < 0.05$). Further, the prevalence of insulin resistance was significantly higher among race/ethnic minorities than non-Hispanic white people.

Multivariate analysis revealed that the cross-sectional association between 25(OH)D and insulin resistance did not vary by age at baseline, diabetes duration, HLA genotype and BMI z-score (each interaction $P \geq 0.1$); thus, the interaction terms were not included in any of the models.

Higher 25(OH)D was significantly inversely associated with insulin resistance (Table 3; model 2), both before and after adjustment for diabetes duration, age, race/ethnicity, gender, insulin regimen, HLA genotype, clinical site and season of clinical visit. Participants who had sufficient levels of 25(OH)D (65 nmol/l) had an adjusted odds ratio of insulin resistance that was 0.70 times that of participants who were at risk of 25(OH)D deficiency (25 nmol/l) (95% CI 0.57– 0.85). Despite smaller sample sizes, because of restriction by design to participants ages ≥ 10 years, separate adjustment for pubertal status (model 3) and physical activity (model 4) yielded similar, statistically significant associations. However, as expected, adjustment for BMI z-score (model 5) in the larger cross-sectional sample resulted in an attenuation of the association (odds ratio 0.81, 95% CI 0.64–1.03). Sensitivity analyses among participants with at least one instance of positive diabetes autoantibodies resulted in similar findings (results not presented).

In parallel analysis using multivariate, linear regression, a 40-unit increase in 25(OH)D was associated with a higher insulin sensitivity score (model 2 covariate adjustment: β-coefficient = 0.50, 95% CI 0.33–0.68, $P < 0.001$). The association was attenuated but remained significant after further adjustment for BMI z-score (β-coefficient = 0.26, 95% CI 0.11–0.40, $P = 0.004$).

Longitudinal sample

The longitudinal sample was similar to the cross-sectional sample at baseline (see Table 1) with respect to gender, HLA risk group, clinical site and season of visit (all $P \geq 0.05$). However, the longitudinal sample had a higher percentage of non-Hispanic white youth (81.4%), was younger (10.3 ± 3.6 years), had higher 25(OH)D (63.0 ± 35.6 nmol/l), insulin sensitivity scores (12.0 ± 2.4) and shorter disease duration (9.0 ± 5.0 months) (all $P < 0.05$) than the cross-sectional sample. For individuals who had insulin sensitivity scores at both the baseline and follow-up examinations, insulin sensitivity scores declined significantly, from mean 12.0 ± 2.4 at baseline to 9.9 ± 2.8 at the follow-up visit ($P < 0.01$), suggesting worsening of insulin sensitivity with Type 1 diabetes progression.

Higher 25(OH)D at baseline was associated with reduced risk for incident insulin resistance at follow-up after adjustment for diabetes duration and time between research visit odds ratio 0.69, 95% CI 0.63–1.14) (Table 4). However, this association was no longer significant after adjustment for other potential confounders. Sensitivity analyses among participants

with at least one instance of positive diabetes autoantibodies, resulted in similar findings (results not presented).

In parallel analysis using multivariate, linear regression, a 40-unit increase in baseline 25(OH)D appeared to be associated with higher insulin sensitivity score in follow-up (model 2 covariate adjustment: β-coefficient = 0.12, 95% CI –0.04 to 0.27), but was not significant $P = 0.15$).

Discussion

In this large cohort of individuals with Type 1 diabetes, nearly half had 25(OH)D < 50.0 nmol/l, with race/ethnic minorities (vs. non-Hispanic white people) and individuals with higher BMI z-score being disproportionately affected. The high proportion of individuals with vitamin D insufficiency is fairly consistent with studies of youth without diabetes [16].

Several cross-sectional studies report an inverse association between vitamin D and insulin resistance [8–11,14,15], but with interesting nuances. Nationally representative data showed an inverse relationship between 25(OH)D and insulin resistance among non-Hispanic white people and Mexican-Americans, but not in non-Hispanic black people, suggesting differential relationship by race/ethnicity [11]. However, our data showed no evidence of effect modification by race/ethnicity. Two other studies observed an inverse association between 25(OH)D and insulin resistance only prior to adjustment for BMI [14,15].

The complex influence of adiposity on the relation between 25(OH)D and insulin resistance remains poorly understood. Obese individuals have lower levels of 25(OH)D than lean individuals [29], which may be related to sequestering and storage of vitamin D in adipose tissue [30]. Alternatively, others report a strong correlation of 25(OH)D in subcutaneous fat and serum [31], suggesting that serum 25(OH)D levels accurately reflect levels in adipose tissue. Given this complex relationship of vitamin D with adipose tissue, and the strong impact of obesity on insulin resistance [2], adjustment in statistical models for BMI may be appropriate if obesity is a confounder, but may also be an over-adjustment to the extent that obesity is involved in relevant biological pathways. In our cross-sectional analysis, adjustment for BMI z-score resulted in an attenuated effect. However, it is not possible to discern if the BMI z-score adjusted result is the best estimate of the true association or if the best estimate is that obtained after adjustment only for potential confounders not including BMI z-score. Additional analyses examining effect modification by obesity status were not significant, suggesting a similar association for individuals who are overweight/obese and normal weight. Understanding the role of adiposity on the relation of 25(OH)D with insulin resistance is an area of great research potential.

The few studies examining the longitudinal association between 25(OH)D and insulin resistance were conducted in older adults and observed inverse associations [12,13]. Our longitudinal analyses revealed that higher 25(OH)D was associated with a lower odds of becoming insulin resistant, although this was not statistically significant after adjustment for potential confounders. The reason for the difference in statistical significance across studies

may be attributed to population differences, sample size or methods to assess insulin resistance.

There are some limitations, as well as strengths, to our study. First, we only have measurements of 25(OH)D and do not have information about 1,25(OH)D, vitamin D binding protein, vitamin D receptors or vitamin D receptor genotype. Additionally, the immunoassay we used to measure 25(OH)D did not distinguish between $25(OH)D_2$ and $25(OH)D_3$; thus, if only one form of 25(OH)D had an effect on insulin resistance, we would have been unable to capture this effect. Second, our analytic sample was limited to individuals who participated in the SEARCH visit and had sufficient availability of stored plasma. However, there is little reason to suppose that the biological relation between 25(OH)D and insulin resistance would differ between participants and non-participants. We repeated our cross-sectional analysis restricted to the longitudinal sample and found identical associations, suggesting no evidence of selection bias. A final limitation is that our findings may be affected by residual confounding; however, several sensitivity analyses were conducted to examine the potential effect of residual confounding by pubertal status and physical activity, finding none.

The strengths of our study include our use of the SEARCH study, a diverse contemporary sample of youth with provider-diagnosed Type 1 diabetes followed prospectively over time. Most research in this area has been conducted using cross-sectional designs and in individuals without diabetes, thus precluding the generalizability of these findings to at-risk populations. The large, well-characterized multi-ethnic sample allowed us to better understand the relationship between vitamin D and insulin resistance in an understudied yet medically vulnerable population. The availability of a validated measure of insulin sensitivity as developed and validated against the gold standard euglycaemic–hyperinsulinaemic clamp [3,22] is a major strength of our study.

In summary, nearly half of individuals with Type 1 diabetes are at risk of deficiency or inadequate levels of vitamin D. Further, although not definitive, our findings suggest that 25(OH)D may impact positively on insulin sensitivity. Future research should utilize additional prospective observational studies and clinical trials to determine the potential clinical relevance of 25(OH)D on insulin sensitivity and related markers of cardiovascular risk among individuals with Type 1 diabetes.

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Abbreviation

25(OH)D 25-dihydroxyvitamin D

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What's new?

- The identification of modifiable factors that improve insulin resistance may be critical for improving long-term health outcomes for individuals with Type 1 diabetes.
- Previous studies examining the relation of vitamin D with insulin resistance have reported inconsistent findings.
- Most research in this area has been conducted using cross-sectional designs and in individuals without diabetes, thus precluding the generalizability of these findings to at-risk populations.
- Determining the relation of vitamin D with insulin in a diverse, contemporary cohort of youth with Type 1 diabetes may have implications for short- and long-term health.

Table 1

Baseline characteristics of youth with Type 1 diabetes diagnosed in 2002–2005 by plasma vitamin D categories: SEARCH Nutrition Ancillary Study (cross-sectional sample, *n* = 1426)

		Plasma vitamin D categories (nmol/l)				
	Total sample	**At risk of deficiency: < 30.0**	**At risk of inadequacy: 30.0–49.9**	**Sufficient: 50.0–125.0**	**Possibly harmful: > 125.0**	***P***
Total sample at baseline, *n* (%)	1426 (100.0)	300 (21.0)	392 (27.5)	667 (46.8)	67 (4.7)	
Race/ethnicity, *n* (%)						< 0.001
Non-Hispanic white	1085 (76.1)	183 (16.9)	286 (26.4)	588 (51.4)	58 (5.4)	
African-American	137 (9.6)	63 (46.0)	43 (31.4)	30 (21.9)	1 (0.7)	
Other	204 (14.3)	54 (26.5)	63 (30.9)	79 (38.7)	8 (3.9)	
Gender, *n* (%)						0.15
Female	696 (48.8)	163 (23.4)	190 (27.3)	314 (45.1)	29 (4.2)	
Male	730 (51.2)	137 (18.8)	202 (27.7)	353 (48.4)	38 (5.2)	
Age at visit (years)	11.2 ± 3.9	12.3 ± 3.9	11.3 ± 3.6	10.9 ± 3.9	10.1 ± 3.4	< 0.001
Insulin sensitivity score	10.5 ± 3.3	9.4 ± 3.5	10.3 ± 3.2	11.0 ± 3.2	11.9 ± 2.8	< 0.001
Insulin resistance (insulin sensitivity score < 8.15), *n* (%)	1057 (74.1)	183 (17.3)	292 (27.6)	525 (49.7)	57 (5.4)	
Insulin sensitive (insulin sensitivity score ≥ 8.15), *n* (%)	369 (25.9)	117 (31.7)	100 (27.1)	142 (38.5)	10 (2.7)	
Diabetes duration (months)	10.2 ± 3.9	11.0 ± 7.2	9.8 ± 6.3	10.0 ± 6.2	9.9 ± 5.9	0.10
HbA_{1c} (mmol/mol)	61 ± 17	61 ± 21	62 ± 15	61 ± 15	61 ± 14	0.23
HbA_{1c} (%)	7.7 ± 1.6	7.9 ± 1.9	7.8 ± 1.4	7.7 ± 1.4	7.7 ± 1.3	0.23
BMI z-score*	0.6 ± 1.0	0.8 ± 1.0	0.6 ± 1.1	0.5 ± 0.9	0.1 ± 0.9	< 0.001
Triglycerides (mg/dl)	66.4 ± 38.5	73.7 ± 44.0	67.6 ± 39.6	63.2 ± 35.4	59.7 ± 30.2	0.0005
Waist circumference	71.0 ± 14.0	75.9 ± 15.1	71.8 ± 14.8	69.0 ± 12.5	64.6 ± 11.1	< 0.001
HLA risk group, *n* (%)†						0.50
Low	702 (51.5)	140 (19.9)	198 (28.2)	334 (47.6)	30 (4.3)	
High/moderate	661 (48.5)	151 (22.8)	180 (27.2)	297 (44.9)	33 (5.0)	
Insulin regimen, *n* (%)‡						0.02
Insulin pump	126 (9.0)	20 (15.9)	27 (21.4)	67 (53.2)	12 (9.5)	
Glargine + rapid-acting insulin	462 (33.0)	98 (21.2)	119 (25.8)	223 (48.3)	22 (4.8)	

	Total sample	Plasma vitamin D categories (nmol/l)				
		At risk of deficiency: < 30.0	**At risk of inadequacy: 30.0–49.9**	**Sufficient: 50.0–125.0**	**Possibly harmful: > 125.0**	***P***
Glargine + 2 or more insulins	100 (7.2)	13 (13.0)	26 (26.0)	53 (53.0)	8 (8.0)	
Multiple injections without glargine	203 (14.5)	40 (19.7)	66 (32.5)	91 (44.8)	6 (3.0)	
Two or fewer insulin injections	508 (36.3)	116 (22.8)	149 (29.3)	224 (44.1)	19 (3.74)	
Clinical SEARCH site, *n* (%)						0.10
South Carolina	263 (18.4)	62 (26.6)	65 (24.7)	120 (45.6)	16 (6.1)	
Ohio	292 (20.5)	62 (21.2)	75 (25.7)	144 (49.3)	11 (3.8)	
Colorado	432 (30.3)	80 (18.5)	124 (28.7)	213 (49.3)	15 (3.5)	
California	131 (9.2)	27 (20.6)	37 (28.3)	60 (45.9)	7 (5.3)	
Washington	275 (19.3)	67 (24.4)	81 (29.5)	114 (41.5)	13 (4.7)	
Hawaii	33 (2.3)	2 (6.1)	10 (30.3)	16 (48.5)	5 (15.2)	
Season of visit, *n* (%)						< 0.001
Winter	369 (25.9)	112 (30.4)	124 (33.6)	130 (35.2)	3 (0.8)	
Spring	357 (25.0)	91 (25.5)	106 (29.7)	141 (39.5)	19 (5.3)	
Summer	392 (27.5)	50 (12.8)	80 (20.4)	233 (59.4)	29 (7.4)	
Autumn	308 (21.6)	47 (15.3)	82 (26.6)	163 (52.9)	16 (5.2)	

Values are mean ± SD, unless specified otherwise.

*10 individuals missing BMI z-score.

†63 individuals missing human leucocyte antigen (HLA) genotype.

‡27 individuals missing insulin regimen.

25(OH)D, 25-dihydroxyvitamin D.

Table 2

Baseline characteristics of youth with Type 1 diabetes diagnosed in 2002–2005 by insulin sensitivity score categories: SEARCH Nutrition Ancillary Study (cross-sectional sample, *n* = 1426)

	Insulin sensitive	**Insulin resistant**	
	Insulin sensitivity score ≥ 8.15	**Insulin sensitivity score < 8.15**	***P***
Total sample at baseline, *n* (%)	1057 (74.1)	369 (25.9)	
Race/ethnicity, *n* (%)			< 0.001
Non-Hispanic white	846 (78.0)	239 (22.0)	
African-American	88 (64.2)	49 (35.8)	
Other	123 (60.3)	81 (39.7)	
Gender, *n* (%)			0.07
Female	501 (72.0)	195 (28.0)	
Male	556 (76.2)	174 (23.8)	
Age at visit (years)	10.3 ± 3.7	14.0 ± 3.0	< 0.001
Plasma vitamin D [(25)-OH, nmol/l]	60.9 ± 35.0	47.8 ± 29.5	< 0.001
Categories of 25(OH)D (nmol/l), *n* (%)			< 0.001
< 30.0	183 (61.0)	117 (39.0)	
30.0–49.9	292 (74.5)	100 (25.5)	
50.0–125.0	525 (78.7)	142 (21.3)	
> 125.0	57 (85.1)	10 (14.9)	
Diabetes duration (months)	9.6 ± 6.2	11.7 ± 7.0	< 0.001
HbA_{1c} (mmol/mol)	57 ± 13	72 ± 22	< 0.001
HbA_{1c} (%)	7.4 ± 1.2	8.7 ± 2.0	< 0.001
BMI z-score*	0.4 ± 0.9	1.2 ± 0.9	< 0.001
Triglycerides (mg/dl)	55.9 ± 23.1	96.7 ± 54.6	< 0.001
Waist circumference (cm)	65.5 ± 9.4	86.8 ± 12.8	< 0.001
HLA risk group, *n* (%)†			0.26
Low	509 (72.5)	193 (27.5)	
High/moderate	497 (75.2)	164 (24.8)	
Insulin regimen, *n* (%)‡			0.26
Insulin pump	95 (75.4)	31 (24.6)	
Glargine + rapid-acting insulin	335 (72.5)	127 (27.5)	
Glargine + 2 or more insulins	76 (76.0)	24 (24.0)	
Multiple injections without glargine	145 (71.4)	58 (28.6)	
Two or fewer insulin injections	396 (78.0)	112 (22.1)	
Clinical SEARCH site, *n* (%)			0.02
South Carolina	194 (73.8)	69 (26.2)	
Ohio	219 (75.0)	73 (25.0)	
Colorado	333 (77.1)	99 (22.9)	
California	87 (66.4)	44 (33.6)	
Washington	206 (75.9)	69 (25.1)	

	Insulin sensitive	**Insulin resistant**	
	Insulin sensitivity score ≥ 8.15	**Insulin sensitivity score < 8.15**	***P***
Hawaii	18 (54.6)	15 (45.5)	
Season of visit, *n* (%)			0.92
Winter	274 (74.3)	95 (25.8)	
Spring	265 (74.2)	92 (25.8)	
Summer	294 (75.0)	98 (25.0)	
Autumn	224 (72.7)	84 (27.3)	

Values are mean ± SD, unless specified otherwise.

[*] 10 individuals missing BMI z-score.

[†] 63 individuals missing human leucocyte antigen (HLA) genotype.

[‡] 27 individuals missing insulin regimen.

25(OH)D, 25-dihydroxyvitamin D.

Table 3

Cross-sectional association between 25-dihydroxyvitamin D [25(OH)D] with prevalent insulin resistance (insulin sensitivity score < 8.15) in youth with Type 1 diabetes diagnosed in 2002–2005: SEARCH Nutrition Ancillary Study*

	Odds ratio (95% CI)†	*n* in model	Covariates included in model
Model 1	0.59 (0.50–0.70)	1426	Diabetes duration
Model 2	0.70 (0.57–0.85)	1338	Diabetes duration, age at baseline, race/ethnicity, gender, insulin regimen, human leucocyte antigen (HLA) genotype, clinical site, season
Model 3	0.74 (0.60–0.92)	824	Model 2 covariates and physical activity[AW1]
Model 4	0.71 (0.56–0.90)	815	Model 2 covariates and Tanner stage
Model 5	0.81 (0.64–1.03)	1330	Model 2 covariates and BMI z-score

*Logistic regression models were used to predict insulin resistance (< 8.15 vs. ≥ 8.15) by 25(OH)D (continuous).

†Odds ratios and 95% confidence intervals were obtained by comparing a difference of 40 nmol/l in 25(OH)D [25(OH)D = 25 nmol/l (at risk of deficiency) vs. 25(OH)D = 65 nmol/l (sufficient)].

Table 4

Longitudinal association between 25-dihydroxyvitamin D [25(OH)D] with incident insulin resistance (insulin sensitivity score < 8.15) in youth with Type 1 diabetes diagnosed in 2002–2005: SEARCH Nutrition Ancillary Study*

	Odds ratio (95% CI)†	*n* in model	Covariates included in model
Model 1	0.69 (0.56–0.84)	735	Diabetes duration at follow-up and time between visits
Model 2	0.85 (0.63–1.14)	698	Diabetes duration at follow-up, time between visits, age at follow-up visit, season of baseline visit, insulin sensitivity score at baseline, race/ethnicity, gender, insulin regimen, human leucocyte antigen (HLA) genotype, clinical site
Model 3	0.86 (0.62–1.21)	361	Model 2 covariates, physical activity at baseline and change in physical activity
Model 4‡	—	34	Model 2 covariates, pubertal status at baseline and change in pubertal status
Model 5	0.88 (0.65–1.20)	690	Model 2 covariates, BMI z-score at baseline and BMI change

*Logistic regression models were used to predict insulin resistance (< 8.15 vs. ≥ 8.15) by 25(OH)D (continuous).

†Odds ratios and 95% confidence intervals were obtained by comparing a difference of 40 nmol/l in 25(OH)D [25(OH)D = 25 nmol/l (at risk of deficiency) vs. 25(OH)D = 65 nmol/l (sufficient)].

‡Model was not fitted because of the small sample size with change in pubertal status measured.